

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 264-204-WO	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/EP2004/051651	International filing date (day/month/year) 29.07.2004	Priority date (day/month/year) 31.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/46, A61P25/00, C07D451/02		
Applicant NEUROSEARCH AS et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 19.03.2005	Date of completion of this report 23.05.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Molina de Alba, J Telephone No. +49 89 2399-7823	



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-12 as originally filed

Claims, Numbers

1-12 received on 19.03.2005 with letter of 19.03.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	12?

2. Citations and explanations (Rule 70.7):**see separate sheet**

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1) Reference is made to the following document:

D1: WO 97/30997 A (NEUROSEARCH AS ; SCHEEL KRUEGER JOERGEN (DK);
MOLDT PETER (DK); WAETJE) 28 August 1997 (1997-08-28)

2) The present application relates to (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts and their use as monoamine neurotransmitter re-uptake inhibitors.

3) Re Item V

3.1 Novelty (Art. 33(2) PCT)

None of the cited documents discloses the particular compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate. The claimed subject-matter is therefore regarded as novel.

3.2 Inventive Step (Art. 33(3) PCT)

D1 is considered to be the closest state of the art. This document relates (cf. abstract and pg. 1, par. 1) to the preparation of particular tropane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors in the treatment of disorders such as Parkinson's disease, depression, obsessive compulsive disorders, panic disorders, dementia, etc. For the preparation of the medicinal compositions, **D1** suggests (cf. pg. 7, par. 1) as pharmaceutically acceptable salts a list of acid addition salts comprising tartrate. It is also mentioned (cf. pg. 8, par. 6), that the resolution of racemic mixtures may be carried out by fractional crystallization of D- or L-tartrates, mandelates, or camphorsulphonates. Example 15 of **D1** discloses the preparation of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane and its citrate salt.

The subject-matter of the application differs from **D1** in that the compound involved is a tartrate and not to a citrate. The Applicant has shown by means of comparative examples (filed on 19.03.2005) that the tartrate of the invention shows much better properties as regards hygroscopicity than its homologous citrate salt. The problem to be solved by the present

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application may thus be regarded as providing **less hygroscopic** salts of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane.

Even though **D1** mentions (see paragraphs indicated above) tartrates among the suitable pharmaceutical salts, this document is silent as to the hygroscopic properties of the resulting substances. Thus, there is no motivation in **D1** for the skilled person to particularly select tartrates among other pharmaceutically acceptable salts. As this selection is accompanied by an unexpected effect (drastically low hygroscopic character) the claimed subject-matter involves an inventive step.

3.3 Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-11.

For the assessment of the present Claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States and the patentability can also be dependent upon the formulation of the claims.